REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

As correctly stated in the Office Action, Claims 1-11 and 16-19 are currently pending. Claims 1-11 and 16-19 stand rejected.

By the present amendment, Claim 3 has been canceled, without prejudice to or disclaimer of the subject matter recited therein. Claims 1 and 4 have been amended to correct typographical errors. Claim 1 has been further amended to recite a D-Pro-D-Val peptide. Support for this amendment can be found, at least on page 5, line 9 of the originally-filed specification. Claim 19 has been amended to be consistent with newly amended Claim 1. New Claim 20 has been added to recite an additional embodiment of the present invention. Support for new Claim 20 can be found, at least, in the specification on page 5, line 8. No new matter has been added by the foregoing. Furthermore, Applicants expressly reserve the right to file a continuation or divisional application to any subject matter canceled by the present amendment.

The presently claimed invention is directed to a method of treating inflammation comprising administering a therapeutically effective amount of peptide comprising the peptide sequence lysine-D-proline-D-valine (Claim 1) or D-lysine-D-Proline-valine (Claim 20). The application has been returned to the Examiner following the a decision from the Board of Patent Appeals and Interferences mailed on August 15, 2002.

Request for Interview

In light of the duration of prosecution of the instant application, Applicants respectfully request an interview with the Examiner to discuss any outstanding rejections in the present case. A Request for Interview is submitted herewith. Should the Examiner deem that the present amendments and arguments put the instant application in condition for allowance, such an interview is of course unnecessary.

Claim Objections

Claim 3 stands objected to under 37 C.F.R. § 1.75(c) as being in improper dependent form. By the present amendment, Claim 3 has been canceled, thereby mooting this objection. Withdrawal of this objection is thus respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-3 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Oluyami et al. (*Eur. J. Pharmacol.* 258:131 (1991)) or Ferreira et al. (U.S. Patent No. 5,389,615) as evidenced by of Applicants' alleged admission, Stedman's Medical Dictionary (24th ed., p. 707-8 and 1218 (1989)), and Oxford Medical Companion (p. 969 (1994)). This rejection is respectfully traversed. Additionally, Claim 3 has been canceled by the present amendment, thereby rendering moot this rejection as it applies to this claim. Initially, Applicants note that Claim 1 has been amended to recite a tripeptide of Lys-D-Pro-D-Val.

Contrary to the Board's decision in the present case, the Examiner has reinstated her rejection of claims 1-3 under 35 U.S.C. § 102(b) as being anticipated by Ferreira et al or Oluyomi et al. The Federal Circuit had held that for prior art to be anticipatory, every element of the claimed invention must be disclosed or suggested, either expressly or inherently, in a single item of prior art in the form literally defined in the claim. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 213 U.S.P.Q. 81, 90 (Fed. Cir. 1986). The only times that additional references may be relied upon in making an anticipation rejection under 35 U.S.C. § 102 is to: (i) prove the primary reference contains an "enabled disclosure;" (ii) explain the meaning of a term used in the primary reference; or (iii) show that a characteristic not disclosed in the primary reference is inherent. *See* M.P.E.P. § 2131.01. It is unclear from the Official Action for which of these three purposes the Examiner uses Applicants' alleged admission, Stedmans's Medical Dictionary, and the Oxford Medical Companion. Moreover, while the Examiner cited to an alleged "admission" on page 1 of the specification, Applicants respectfully submit that the Examiner never stated what it is that she believes is an admission or explains which of the only three purposes for which the alleged "admission" could be used in connection with the disclosures of the Ferreira et al. or Oluyomi et al. references. Applicants respectfully assert that the rejections over Ferreira et al. or Oluyomi et al. are in error and respectfully ask that it be withdrawn in accordance with the August 15, 2002 decision of the Board.

As stated at page 1 of the specification of the present application, "inflammation is a set of biological reactions which exist throughout the animal kingdom." Inflammation

"may be defined as the first response to any local attack by a series of non-specific reactions triggered whatever the initial cause and occurring in three steps: vascular, cellulo-vascular and tissue fibrosis. Swelling, pain, redness and warmth are the terms which may be used to describe localized inflammation." *See* specification, page 1. Nothing in this description necessarily equates inflammation with pain.

Claim 1 requires a peptide that is Lys-D-Pro-D-Val. New Claim 20 requires a peptide that is D-Lys-D-Pro-Val. Neither of these anti-inflammatory peptides are disclosed or suggested by Oluyami et al., which is directed solely to anti-nociception and which does not disclose these particular optical isomeric peptides. Similarly, Ferriera et al. does not disclose or suggest a Lys-D-Pro-D-Val peptide or a D-Lys-D-Pro-Val peptide. *See, e.g.*, col. 2, l. 46-52. Moreover, nothing in either disclosure leads to the use of the Lys-D-Pro-D-Val or D-Lys-D-Pro-Val peptides for treating inflammation because neither reference mentions the treatment of inflammation.

As the Board found, Ferreira et al. and Oluyomi et al. disclose that a lysine-D-proline-valine peptide possesses analgesic activity. The references also suggest that the compound may be useful in a method of treating or alleviating pain. As the Board found, however, relying on the Mahe Declaration, "treating pain . . . is not equivalent with or identical to treating inflammation." *See* Decision at 4. Applicants are hard-pressed to see how, in contraindication from the Board, the Examiner can reinstate this rejection based on the argumentation found in the current Official Action. A compound considered to treat

pain is not necessarily considered an anti-inflammatory agent. Alternatively, a compound which treats inflammation does not necessarily treat pain.

To anticipate a claim under 35 U.S.C. § 102, a reference must disclose or suggest each and every claim element. As is demonstrated above, this is not the case in the present rejection. Accordingly, Applicants respectfully submit that the Examiner has not established a case of anticipation. Withdrawal of this rejection is respectfully requested.

Claims 1-3 and 5-10 stand rejected under 35 U.S.C. § 102(b) as anticipated by Hiltz et al. (*Peptides* 12:767 (1991)). This rejection is respectfully traversed. Additionally, Claim 3 has been canceled by the present amendment, thereby rendering moot this rejection as it applies to this claim.

As with Ferreira et al. and Oluyami et al. above, the particular tripeptides of Claim 1 and new Claim 20 are not disclosed by Hiltz et al. Moreover, the data of Hiltz et al. disclose that a peptide wherein proline is in D form is **not effective** in treating inflammation. Applicants note that the Board was likely relying on a typographical error in stating that the data in Table 1 of Hiltz et al. contradicts Applicants' position that Hiltz et al. suggest that a D-Pro peptide is not effective as an anti-inflammatory. *See* Board Decision, p. 7. Although the fourth set of data in Table 1 indicate that the peptide is Ac-[D-**Pro**^{13}]α-MSH (11-13)-NH_2, a review of p. 768, col. 2, ll. 17-22, of Hiltz et al. clearly indicate that this is a typographical error and should read Ac-[D-**Val**^{13}]α-MSH (11-13)-

NH_2. The data for the D-Pro peptide (Ac-[D-Pro^{12}]α-MSH (11-13)-NH_2 in Table 1 clearly show that this peptide elicited no significant effect ($p < 0.65$) on inflammation.

Not only does Hiltz et al. fail to disclose or suggest D-Lys-D-Pro-Val or Lys-D-Pro-D-Val peptides for treating inflammation, but Hiltz et al. **expressly teach away** from such peptides. In this regard, Hiltz et al. particularly disparage D-Pro peptides (p. 770, col. 2, ll. 1-8) and on page 770, col. 2, ll. 24-26 state, "[t]his finding underlines again the importance of L-Pro to the anti-inflammatory response."

With regard to Claims 5-10, because Hiltz et al. fail to disclose or suggest the presently claimed peptides, Hiltz et al. also cannot disclose or suggest protective group modifications of the claimed peptides or effective doses.

In view of the above, Hiltz et al. does not anticipate, or render obvious, the presently claimed invention. Thus, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-4 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Ferreira et al. in view of Applicants' alleged admission, Stedman's Medical Dictionary and Oxford Medical Companion. This rejection is respectfully traversed. Additionally, Claim 3 has been canceled by the present amendment, thereby rendering moot this rejection as it applies to this claim.

On page 7 of the Official Action, the Examiner states "the reference clearly suggests the making and the use of Dlys-Dpro-Dval (preferred embodiment)." Applicants

respectfully request that the Examiner explicitly point out where the Ferriera et al. publication expressly suggests such a peptide. Applicants respectfully submit that Ferreira et al. do not disclose or suggest any of the Lys-D-Pro-D-Val (Claim 1), D-Lys-D-Pro-Val (Claim 20), or D-Lys-D-Pro-D-Val (Claim 4) peptides.

Additionally, as discussed above and as clearly recognized by the Board, Ferreira et al. is solely directed to the treatment of pain. Moreover, one skilled in the art interested in treating inflammation with peptides would not be motivated to use the claimed peptides because Hiltz et al. (Peptides 12:767-771, (1991)), which the Board found to be the closest art to the presently claimed invention, expressly teach away from using D-Pro peptides to treat inflammation. Accordingly, Applicants respectfully submit that any of the cited publications, either alone or in combination, render the presently claimed invention obvious.

Applicants are puzzled by the Examiner's comments on page 7 concerning dosages as no claims directed to dosages are included in this rejection.

Because the references and alleged "admission" as combined by the Examiner fail to disclose or suggest the invention as claimed, withdrawal of this rejection is respectfully requested.

Claims 1-6 and 19 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ferreira et al., Applicants' alleged admission, Stedman's Medical Dictionary, and Oxford Medical Companion in view of Lipton et al. (U.S. Patent No.

5,157,023) and Oluyami et al. This rejection is respectfully traversed. Additionally, Claim 3 has been canceled by the present amendment, thereby rendering moot this rejection as it applies to this claim.

Applicants reiterate their position stated above that neither Ferriera et al. nor Oluyami et al. disclose or suggest the presently claimed peptides, Lys-D-Pro-D-Val (Claim 1), D-Lys-D-Pro-Val (Claim 20), D-Lys-D-Pro-D-Val (Claim 4), or (acidyl-(D)Lys-(D)Pro-(D)Val-NH_2 (Claim 19). Moreover, as discussed above and as recognized by the Board, neither Ferreira et al. nor Oluyami et al. are directed to treating inflammation. Lipton et al. merely concerns the use of protected forms of Lys-Pro-Val peptides, wherein the amino acids are in the L configuration. Accordingly, none of the cited references can render the presently claimed invention obvious because they fail to disclose or suggest the presently claimed peptides. Also, as discussed above, the closest prior art in the Board's opinion, Hiltz et al., expressly teaches away from the use of D-Pro peptides for treating inflammation, further demonstrating the non-obviousness of the presently claimed invention.

Because the rejection fails to establish a *prima facie* case of obviousness, withdrawal of this rejection is respectfully requested.

Claims 1-11 and 16-19 stand rejected under 35 U.S.C. § 103(a) as purportedly obvious over Ferreira et al., Stedman's Medical Dictionary, Oxford Medical Companion in view of Nordlund et al. (U.S. Patent No. 4,874,744), Lipton et al., and Remington's

Pharmaceutical Science (ch. 87 and 92) and Oluyami et al. This rejection is respectfully traversed. Additionally, Claim 3 has been canceled by the present amendment, thereby rendering moot this rejection as it applies to this claim.

Applicants reiterate their position discussed above that Ferriera et al., Oluyami et al, and Lipton et al. do not disclose or suggest the particular presently claimed peptides (Lys-D-Pro-D-Val (Claim 1), D-Lys-D-Pro-Val (Claim 20), D-Lys-D-Pro-D-Val (Claim 4), or (acidyl-(D)Lys-(D)Pro-(D)Val-NH_2 (Claim 19)). Additionally, Nordlund et al. do not disclose or suggest these particular peptides either. In fact, the Nordlund et al. publication does not mention optical isomers at all, much less the particular isomers presently claimed. Thus, Applicants respectfully submit that the presently claimed peptides are not disclosed or suggested by any of the cited publications, either alone or in combination. Therefore, Applicants respectfully submit that Claims 1, 2, 4, 19, and 20 are not obvious. In view of the fact that none of the cited publications disclose or suggest the particular peptides, none of the publications can disclose or suggest the appropriate dosages or the use of protecting groups with respect to these peptides. Accordingly, Applicants respectfully submit that Claims 5-11 are not obvious.

Applicants further submit that the combination of these references is improper. The Ferriera reference does not suggest the use of the tripeptide for inflammation, but rather pain control. In particular, Ferreira et al. disclose the use of internal administration (*e.g.*, orally or parenterally), not topical administration, and highlights the benefits of the peptides as not causing gastric effects like other known analgesics. *See* col. 4, ll. 48-65.

Applicants respectfully submit that there is no motivation to combine either the Ferriera et al. or Oluyami et al. publications, which deal with pain or antinociception, with Nordlund et al., which deals with treating dermatitis. Therefore, topical application is not obvious. The Hiltz et al. publication, deemed to be the closest art to the presently claimed invention by the Board, demonstrates that the Lys-D-Pro-Val peptide is ineffective for treating inflammation. Accordingly, one skilled in the art would not be motivated to topical application of D-Pro peptides for inflammation, much less the particular peptides of the presently claimed invention. Therefore, with regard to Claims 16-17, Applicants respectfully submit that the topical application of the presently claimed peptides is non-obvious.

Claim 18 requires that the composition further comprise an effective anti-inflammatory amount of at least one glucocorticoid, vitamin D or derivative thereof, and/or a non-steroidal anti-inflammatory agent. Applicants respectfully reject outright the Examiner's statement that "the combination of two or more known agents to treat a disease is within the purview of one skilled in the art" as rendering the presently claimed invention obvious. Office Action, p. 10. Applicants respectfully submit that this generic statement is woefully insufficient to render obvious the combination of a **particular** group of peptides with another anti-inflammatory agent to treat inflammation. The cited art must suggest the desirability of the particular combination. *See, e.g.*, M.P.E.P. § 2143.01 (and references cited therein). The Examiner has merely made a statement that is not specific to the presently claimed invention. Therefore, in addition to the arguments above that the

presently claimed peptides are not obvious, Applicants respectfully submit that the Examiner has not met the burden of setting forth a *prima facie* case of obviousness for at least Claim 18.

Because the rejection fails to establish a *prima facie* case of obviousness, withdrawal of this rejection is respectfully requested.

Claims 1-3, 5-11, and 16-19 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Oluyami et al., Applicant's alleged admission, Stedman's Medical Dictionary, and the Oxford Medical Companion, in view of Nordlund et al., Lipton et al., and Remington's Pharmaceutical Science. This rejection is respectfully traversed. Additionally, Claim 3 has been canceled by the present amendment, thereby rendering moot this rejection as it applies to this claim.

Applicants reiterate their position discussed above that Oluyami et al, Lipton et al., and Nordlund et al. do not disclose or suggest the particular presently claimed peptides: Lys-D-Pro-D-Val (Claim 1), D-Lys-D-Pro-Val (Claim 20), D-Lys-D-Pro-D-Val (Claim 4), or (acidyl-(D)Lys-(D)Pro-(D)Val-NH_2 (Claim 19). Thus, Applicants respectfully submit that the presently claimed peptides are not disclosed or suggested by any of the cited publications, either alone or in combination. Therefore, Applicants respectfully submit that Claims 1, 2, 19, and 20 are not obvious. In view of the fact that none of the cited publications disclose or suggest the particular peptides, none of the publications can disclose or suggest the appropriate dosages, the use of protecting groups, or formulations

with respect to these peptides. Accordingly, Applicants respectfully submit that Claims 5-11 are not obvious.

Applicants further submit that the combination of these references is improper. The Oluyami et al. reference does not suggest the use of tripeptides for inflammation, but rather anti-nociception. In particular, Oluyami et al. disclose the use of internal administration (*e.g.*, oral or i.p. administration), not topical administration. *See* abstract. Applicants respectfully submit that there is not motivation to combine Oluyami et al. publication, which deals with antinociception, with Nordlund et al., which deals with treating dermatitis. Therefore, topical application is not obvious. The Hiltz et al. publication, deemed to be the closest art to the presently claimed invention by the Board, demonstrates that the Lys-D-Pro-Val peptide is ineffective for treating inflammation. Accordingly, one skilled in the art would not be motivated to use topical application of the presently claimed peptides for inflammation. Therefore, with regard to Claims 16-17, Applicants respectfully submit that the topical application of the presently claimed peptides is non-obvious.

Claim 18 requires that the composition further comprise an effective anti-inflammatory amount of at least one glucocorticoid, vitamin D or derivative thereof, and/or a non-steroidal anti-inflammatory agent. Applicants respectfully reject outright the Examiner's statement that "the combination of two or more known agents to treat a disease is within the purview of one skilled in the art" as rendering the presently claimed invention obvious. Office Action, p. 12. Applicants respectfully submit that this generic statement

is woefully insufficient to render obvious the combination of a **particular** group of peptides with another anti-inflammatory agent to treat inflammation. The cited art must suggest the desirability of the particular combination. *See, e.g.*, M.P.E.P. § 2143.01 (and references cited therein). The Examiner has merely made a statement that is not specific to the presently claimed invention. Therefore, in addition to the arguments above that the presently claimed peptides are not obvious, Applicants respectfully submit that the Examiner has not met the burden of setting forth a *prima facie* case of obviousness for at least Claim 18.

Because the rejection fails to establish a *prima facie* case of obviousness, withdrawal of this rejection is respectfully requested.

Claims 1-11 and 16-19 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Hiltz et al. in view of Nordlund et al., Lipton et al., and Remington's Pharmaceutical Science. This rejection is respectfully traversed. Additionally, Claim 3 had been canceled by the presently claimed amendment, thereby rendering moot this rejection as it applies to this claim.

Applicants respectfully submit that the particular tripeptides of Claims 1, 2, 4, 19, and new Claim 20 are not disclosed or suggested by Hiltz et al. Moreover, the data of Hiltz et al. disclose that a peptide wherein proline is in D form is **not effective** in treating inflammation. Applicants note that the Board was likely relying on a typographical error in stating that the data in Table 1 of Hiltz et al. contradicts Applicants' position that Hiltz

et al. suggest that a D-Pro peptide is not effective as an anti-inflammatory. *See* Board Decision, p. 7. Although the fourth set of data in Table 1 indicate that the peptide is Ac-[D-**Pro**^{13}]α-MSH (11-13)-NH_2, a review of p. 768, col. 2, lines 17-22, of Hiltz et al. clearly indicate that this is a typographical error and should read Ac-[D-**Val**^{13}]α-MSH (11-13)-NH_2. The data for the D-Pro peptide (Ac-[D-Pro^{12}]α-MSH (11-13)-NH_2) in Table 1 clearly show that this peptide caused no significant effect ($p < 0.65$).

Not only does Hiltz et al. fail to disclose or suggest the Lys-D-Pro-D-Val (Claim 1), D-Lys-D-Pro-Val (Claim 20), D-Lys-D-Pro-D-Val (Claim 4), or (acidyl-(D)Lys-(D)Pro-(D)Val-NH_2 (Claim 19) peptides for treating inflammation, but Hiltz et al. **expressly teach away** from such peptides. Hiltz et al. particularly disparage D-Pro peptides (p. 770, col. 2, ll. 1-8) and on page 770, col. 2, ll. 24-26 state, "[t]his finding underlines again the importance of L-Pro to the anti-inflammatory response."

With regard to Claims 5-11, because Hiltz et al. fail to disclose or suggest the presently claimed peptides, Hiltz et al. also cannot disclose or suggest protective group modifications of the presently claimed peptides, effective doses, or formulations. Therefore, Hiltz et al. cannot anticipate or render obvious the presently claimed invention.

With regard to Claims 16-17, the Hiltz et al. publication does not disclose or suggest the presently claimed peptides and in fact teaches away from them. Accordingly, one skilled in the art would not be motivated to administer the presently claimed peptides to treat inflammation **at all**, much less **topically** administer the presently claimed peptides.

Claim 18 requires that the composition further comprise an effective anti-inflammatory amount of at least one glucocorticoid, vitamin D or derivative thereof, and/or a non-steroidal anti-inflammatory agent. Applicants respectfully reject outright the Examiner's statement that "the combination of two or more known agents to treat a disease is within the purview of one skilled in the art" as rendering the presently claimed invention obvious. Office Action, p. 13. Applicants respectfully submit that this generic statement is woefully insufficient to render obvious the combination of a **particular** group of peptides with another anti-inflammatory agent to treat inflammation. The cited art must suggest the desirability of the particular combination. *See, e.g.*, M.P.E.P. § 2143.01 (and references cited therein). The Examiner has merely made a statement that is not specific to the presently claimed invention. Therefore, in addition to the arguments above that the presently claimed peptides are not obvious, Applicants respectfully submit that the Examiner has not met the burden of setting forth a *prima facie* case of obviousness for at least Claim 18.

Because the rejection fails to establish a *prima facie* case of obviousness, withdrawal of this rejection is respectfully requested.

Conclusions

From the foregoing, further and favorable consideration of the subject application in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this Amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned attorney so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: September 25, 2003

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